

SPL Process ER/DL Meeting Meeting Minutes Oct 19, 2016 (final FDA responses)

Chair of today's meeting: Pat Cowall

Teleconference information:

USA Toll-Free: 866-213-2145

USA Paid/International: 609-454-9913

Access code: 273 8216

Link to the SPL wiki:

<http://spl-work-group.wikispaces.com/share/view/51351516>

Agenda:

Presentations from FDA Guests (presentations attached):

Final Rule effective Nov 29, 2016: Leyla Rahjou-Esfandiary, FDA DRLS

Common SPL mistakes – as identified by FDA DRLS: Paul Loebach, FDA DRLS

Additonal Resource:

- FDA (CDER SBIA) webinar on Establishment Registration and Drug Listing – overview of DER, DL and the final rule
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm521365.htm>

Questions with Responses – from meeting:

1. Timing for implementation of the new Final Rule requirement for updating Drug Listings every 6 months.

- The effective date for the Final Rule is November 29, 2016. The Final Rule states that drug listings must be updated “...no later than the time when listing information is due after the first anniversary of the effective date of this final rule [i.e., in December 2017].”

FDA Response:

- Implementation is required 1 year after effective date – ie during Oct-Dec 2017
- FDA's intent is that registrants submit updated drug listings throughout the calendar year
- If nothing has changed, registrants must submit an “no change” update during the Oct – Dec annual registration timeframe (same as DERs.)
- FDA is still working on the exact logistics on how the “no change” submission will be done if there are no updates to drug listings.

FINAL

2. **Update to DLs** - **How:** Please explain the logistics of how this should happen for the following scenarios:

- If nothing changed in any of the drug listings for a company/labeler.
- If some DLs changes, but most DLs have not changed in the 6 months.
- If the labeler code information has changed during the 6 months and also needs to be updated.
- API, bulk, and in process drug listings

FDA Response:

- Stay tuned for more information.
- FDA is currently developing the mechanism through which the no change certification is submitted to the agency.
- FDA will communicate this in 2017, prior to the annual update period of Oct to Dec, 2017.
- The SPL process team will update these minutes with the process once it has been communicated by FDA.

3. **No change notification for private label distributors:**

- There is one labeler code request file (one set ID) for each private label distributor.
- The PLD has product manufactured by multiple contract manufacturers.
- If manufacturer A has submitted the initial labeler code request on behalf of a private label distributor (PLD), that manufacturer wouldn't be able to vouch that ALL other manufacturer drug listings for that private label distributor are compliant with the June and December dates.
- How would this be managed?

FDA Response:

Stay tuned for more information about the "no change" process.

4. **When to update a labeler code:** After a labeler code has been assigned, should a labeler update the optional information included in an NDC Labeler Code request (such as facility address and business operation(s))? For example, after assignment and registration of a labeler code should the NDC Labeler Code file be updated:

- To show the labeler has added an operation (was a manufacturer and is now a distributor) or qualifier (operation was for OTC products now operation is also for prescription products).
- to give the new address for the facility

FDA Response:

- [Provided by Paul to Howard Shatz on 10/6/2016]: Yes to both questions, though it is not specifically required by regulation. We recommend it (and greatly appreciate it) since we use this information for official FDA communications regarding listing. Specifically for updating the address, if the address provided and linked with the labeler code is that of the facility, then yes it should change if the address of the registered facility changes.

5. **Market end date- when to add** – when to enter into SPL: If a product has been discontinued do we need to put a ‘marketing end date’ in the SPL showing the last lot expiration date and list at the time of discontinuation or can we list with the ‘marketing end date’ at time of expiration.

FDA Response:

- FDA preference is to have it added as soon as possible after you know that marketing has ended. You can enter a future market end date.
- The preferred date should be the “last lot expiration date.”

6. **Market end dates- do we need to enter two dates -- end of distribution and last lot expiration:** As part of 207.57 (b)(1)(ii) it indicates that 2 dates are necessary – 1) for the discontinuation of manufacture and 1) for the date of the expiration of the last lot.

(ii) Submit the date that they discontinued the manufacture, repacking, relabeling or salvaging for commercial distribution of a listed drug and provide the expiration date of the last lot manufactured, repacked, relabeled, or salvaged;

Please discuss what fields in the SPL file are being used to differentiate these 2 dates.

- The last lot expiration is often several months/years after the discontinuation of manufacturing. Is this being interpreted that once manufacturing is discontinued, the listing should be updated in the next June or December timeframe to include the end of manufacturing date and the last lot expiration date at that time?

- Are companies using the drug product level marketing status and date to record the end of manufacturing (which would be several months prior to the expiration)?
- Are companies using the package level marketing status and dates to record the expiration date of the last lot which is equal to the marketing end date?
- Is there any impact to a drug being available for reimbursement and on the NDC Directory if an end of manufacturing date is entered?

FDA Response:

- FDA intends that there be one date, preferably the expiration date of the last lot.
- This date determines when the drug is removed from the NDC directory.

7. Product changes that require a new NDC code:

Please confirm that when an inactive ingredients changes in a formulation, that no update related to that NDC is needed (or that a replacement NDC is needed).

- This may be a concern, in that inactive ingredients can cause allergies and intolerances. Compendia rely on knowing, by NDC, these ingredients so that the compendia can codify allergy screening for use in EHRs. This could become even more relevant with the emerging biosimilars.

FDA Response:

- Change of inactive ingredients do not require a new product NDC code.
 - o See slide 6 in Final Rule presentation
 - o See 21 CFR 207.35

8. Reuse of NDC codes (also see question 20 below):

Can NDC codes ever be reused? In the past, 21CFR207 stated that codes could be reused after 5 years of inactivation.

FDA Response:

- No. NDC codes cannot be reused.
- See slide 6 in Final Rule presentation
- 21 CFR 207 states that NDC codes must be unique
- If there is a question about NDC codes that have been used in the past, a registrant can request a listing of the NDC codes that have been used for a particular labeler code.
- As a part of good practice, FDA recommends that each labeler keep track of which NDC codes are in use (and have been used in the past).

Questions and Responses - Post meeting notes:

9. “Active pharmaceutical ingredient” and “bulk drug substance”

- The definition of bulk drug substance states it is the same as active pharmaceutical ingredient. The definition of API states it is ANY substance intended to furnish the pharmacological activity in diagnosis, cure, mitigation, treatment or prevention of disease...My question is that I was always under the understanding that there were certain “atypical APIs” in which there was enforcement discretion in whether these atypical APIs had to be produced under GMP conditions and in registered facilities. For example, isopropyl alcohol that is often produced in a refinery-type plant may not be produced in an FDA-registered facility. Under this definition, ALL APIs would need to come from registered facilities, be listed and the API NDC would need to be included as part our drug listing, is that correct?

FDA response:

It is not very clear what you mean by an “atypical API”. If you’re implying to products that have many different commercial applications, any substance which ends up to be an active ingredient in a drug, is considered an API. In such cases, all the applicable laws for APIs and API manufacturers apply.

- Is it required to list API manufacturer for OTC monograph products under this rule?

FDA response:

It is required for the API manufacturer of an OTC monograph drug to be included on the OTC drug listing SPL.

10. Who is responsible for Drug Listing – Manufacturer or PLD:

The manufacturer/registrant is responsible for drug listing. This includes contract manufacturing. If we are a private label manufacturer and have our product produced at a contract manufacturer, does that drug listing have to include two NDC’s (one from the contract manufacturer and one from the private label distributor) or is it still sufficient to just list the contract manufacturer as the manufacture site of the product and only include our private label distributor’s NDC in the listing?

FDA response:

- With respect to private label distributors (PLDs), under § 207.17(b), PLDs who do not also manufacture, repack, relabel or salvage drugs are not required to register. FDA will accept listing information submitted by a PLD only if it is acting as an authorized agent for the registered establishment (in this case contract manufacturer organization or CMO) that manufactures, repacks, relabels or salvages drugs.
- If the PLD does not elect to list the PLDs drug, the registered establishment is responsible for listing the drug, and must use a Labeler Code that uniquely identifies the PLD for which it manufactures or processes the drug under § 207.33(c).

- If the PLD does elect to list the drug, then it does so as an authorized agent for the registered establishment, however, legal responsibility for complying with this final rule does not transfer from the manufacturer, repacker, relabeler, or salvager. When a PLD elects to list its drug product – identified by the PLD’s own NDC and label – FDA would not also expect the manufacturer to list that NDC a second time, but would nonetheless require the manufacturer to list the product it manufactures for the PLD, identified with the manufacturer’s own NDC. This is regardless of whether the drug is also marketed under the contract manufacturer’s name or solely under the PLD’s name.

11. Products with multiple NDCs. Please provide an example for clarification

FDA response:

If a drug is manufactured by a contract manufacturer for a private label distributor, there should be two SPL drug listings, using different NDC codes:

- PLD using the PLD labeler code and full content of labeling.
- CMO using the CMO labeler code. The CMO’s drug should be listed under an “Exclusively Manufactured for PLD” Marketing Category, using the CMO’s labeler code. This SPL does not require the inclusion of full Content of Labeling (ie a PI).

12. Listing requirements for manufacturers who make the same product for multiple PLDs.

On Slide 15 of the Top 10 Common Errors presentation from the 10/19 meeting, the last bullet stated: *“If a manufacturer makes an identical product for multiple PLDs, it need only list the product once under a single NDC with its own labeler code. However, we expect a unique NDC from each PLD for their version of the product.”* Can you explain this? I am thinking this may not change much for us, we currently list any products under our own NDC we distribute under our house brand name and separate listings for each PLD, but want to make sure I’m correct.

FDA response:

In the previous question, FDA said they expect to see a submission from both the CMO and the PLD. However, if that CMO makes the same product for a second PLD, the CMO does not have to submit a second listing, so long as the product is exactly the same. However each PLD version must have a separate listing.

Outstanding questions:

13. Please clarify the text in 207.41 underlined below.

§207.41 Who must list drugs and what drugs must they list?

Each registrant must list each drug that it manufactures, repacks, relabels, or salvages for commercial distribution. Each domestic registrant must list each such drug regardless of whether the drug enters interstate commerce.

Since drug listing is for commercial distribution, can you give examples for which a registrant would need to drug list a drug that does not enter interstate commerce.

FDA Response:

- The intent of this statement is to convey that all drugs must be drug listed REGARDLESS of whether it crosses state lines. Drugs which are manufactured and sold locally also must be drug listed.

14. Which establishments need to be included in the drug listing?

What establishments are required by FDA to be listed in the drug listing of a product and its packages (ie. what business operations are required)? FDA's 'Step-by-Step Instructions for Creating Structured Product Labeling (SPL) Files for Drug Establishment Registration and Drug Listing' states 'the establishments are the entities involved in the manufacturing or processing the drug product' but do all establishments involved need to be listed? Also, establishments that perform only stability or analysis testing, are they required to be included in the drug listing?

FDA Response:

- 21 CFR 207.49(a)(12)(ii): The name and Unique Facility Identifier of every establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment
 - o Ie This includes, but is not limited to, API manufacturer, manufacturer, pack and label company, (if different than the manufacturer), analysis.
 - o Ie any establishment included in the manufacturing process, including contract manufacturers, sterilizers, control labs, etc.

15. Which “manufacturers” are required to submit drug listing?

- 207.41 states that every manufacturers are required to drug list.
- In the past, this was interpreted to be manufactures that participated in the API manufacturing or transforming of the API into in process or finished product.
- Per definitions in 207.1 of manufacturer, analytical labs, etc. are also called out.

Questions:

- What is FDA interpretation of what types of manufacturers are required to submit drug listing?
- Are analytical labs, sterilizers, etc now required to submit a drug listing SPL file? If so, If the answer to the previous question is yes, then we will have a new group of companies to train in creating SPL. What does their SPL look like? In particular, what would be their content of labeling?
 - o Sterilizers are shipped product to sterilize. What is their COL – ie drum label of the sterilized product?
 - o Analytical lab would only be shipped small samples of the product? What would they use for content of labeling?

FDA Response:

- Establishments who **do** need to drug list: Establishments who do **any** manufacturing step/processing on the actual product.
 - o If an establishment is not the final marketer, they should use a marketing category of one of the following:
 - DRUG FOR FURTHER PROCESSING (for unfinished/bulk product only)
 - APPROVED DRUG PRODUCT MANUFACTURED EXCLUSIVELY FOR PRIVATE LABEL DISTRIBUTOR
 - OTC MONOGRAPH DRUG PRODUCT MANUFACTURED EXCLUSIVELY FOR PRIVATE LABEL DISTRIBUTOR
 - UNAPPROVED DRUG PRODUCT MANUFACTURED EXCLUSIVELY FOR PRIVATE LABEL DISTRIBUTOR
 - o COL: submit a picture (jpg) of the label that is on the product that goes out the door (ie the label on the drum). This label should either:
 - Include the NDC code with their own labeler code (eg for the contract manufacturers)
OR
 - No NDC on the label at all.

This label should NOT have the PLD (final) NDC on it.
- Establishments who **do not** do a processing step on the actual product (eg control labs test only samples sent to them by a manufacturer) .
 - o Examples: Analytical/control labs

16. How to submit annual update for drug listing - related to question #2 above:

- Can we use CDER Direct to submit this blanket registration on labeler code (using the labeler code request update) and just create a new version with no changes if there aren't any? And if I understood correctly, this will cause any drug listing for this labeler code that hasn't been updated that year to be in compliance with the Final Rule requirement. There's no need to send a new version of the drug listing. Please confirm.
- If we choose the option to submit labeler code updates instead of individual drug listings by product, is there a way to determine it has been updated other than receiving the successfully submitted message upon submission? In other words, I usually check FDA's 'Drug Establishments Current Registration Site' when I successfully submit an establishment registration to ensure it did get updated on their website. Is there any FDA website where we can check for labeler code updates

FDA Response:

- Stay tuned for more information. FDA intends to add functionality -- however they decide to implement.
- Implementation date: Oct to Dec, 2017.
- We will provide an answer in SPL Team meeting/ minutes prior to the implementation period.

17. Can NDCs be reused if it's the same pkg for that product that comes back into the market (everything is the same as far as the ingredients of the product)?

FDA Response:

- §207.37 What restrictions pertain to the use of the NDC?
- (b) If marketing is resumed for a discontinued drug, and no changes have been made to the drug that would require a new NDC under §207.35, the drug must have the same NDC that was assigned to it as described in §207.33, before marketing was discontinued.
- If you are marketing the exact same product, you **should** use the same NDC code.

18. If we have a 'kit' which contains the drug product, an applicator, and 'water', we still do not assign an NDC to 'water'?

FDA Response:

- Sterile water for injection (ie diluent) has to have an NDC.
- Other water (distilled water used for mixing an oral solution/suspension) does not have an NDC code.
- CDER Kit components: If any kit component is marketed on its own, it should have an NDC on the kit component.
- CBER requires an NDC on every package level.

19. Is a new NDC product code required by the private label distributor for a change in manufacturer?

FDA Response:

- No. Refer to reasons for assigning a new NDC product code provided in §207.35 What changes require a new NDC?
- If a feature listed in 207.35 changes, then a new NDC code is needed.
- If nothing else changes, the same NDC should be used.

20. Drug listing of inactive ingredients (even though may be flagged confidential).

What is the agency's view on crossing the line with proprietary formulation information?

If the actives & inactives are listed—it is pretty close to sharing a formulation.

If listing the inactive are mandated, would it be possible to not share the strengths/concentrations?

FDA Response:

- Be sure to mark the inactives as confidential and the inactives will not show.
- FDA uses the confidentiality flag to redact this information before publishing to Daily Med or on FDA sites.

21. Problems with Non-Proprietary Name field, (reference slide 13 of the Common SPL Errors

Experienced by FDA DRLS (Paul Loebach))

If commas are an error when there is more than one active ingredient used in the non-proprietary name, how should we separate each one?

FDA Response:

- The issue is the inconsistency of notation in separating multiple ingredients.
- When there are multiple active ingredients, FDA recommends that they be listed in the same order in the product name, nonproprietary name, list of ingredients, etc.

22. Where can we get a list of all NDC numbers that have been used (refer to Question 8 above):

When looking for NDC numbers on the FDA NDC database and we are unable to locate them, is there an archival resource to confirm NDC#s that have been previously assigned so we can avoid duplicate numbers?

FDA Response:

- Any company can request a list of past and presently assigned NDC codes.

23. Please clarify which scenarios are Paul and Leyla able to over-ride SPLs and which should go to Lonnie Smith.

FDA Response:

- You can approach either Lonnie or eDRLS. They will advise if the other group should be contacted instead.
- Technical SPL issues are typically handled by Lonnie.
- If it is a regulatory issue, it will need to go to eDRLS.